

specification. Support for claims 25-26 can be found e.g., on page 4 of the specification and in original claim 6. Support for claims 27-29 can be found e.g., on page 13 of the present specification. Support for claims 30-31 can be found e.g., on page 14 of the present specification. No new matter has been added. The additional claims will not necessitate any further searching by the Examiner.

#### **FORMAL DRAWINGS**

Applicants filed a Submission of Formal Drawings on June 15, 2001. The Examiner has not yet indicated whether these formal drawings have been approved. Applicants hereby request the Examiner to indicate whether these drawings have been approved.

#### **CLAIM FOR PRIORITY**

Applicants request that the Examiner acknowledge the claim to priority of U.S. Application No. 08/212,629, filed March 14, 1994.

#### **REJECTION UNDER 35 U.S.C. § 103**

The Examiner rejected claims 16-20 under 35 U.S.C. §103(a) over Feldman (*Progress in Growth Factor Research*, Vol. 4: 247-255, 1992) in view of Trinchieri (*Progress in Growth Factor Research*, Vol. 4: 355-368, 1992). Applicants traverse the rejection for the reasons presented below.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim elements. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in

the art, to modify the reference or to combine reference teachings. Finally, there must be a reasonable expectation of success. M.P.E.P. § 2143 (7<sup>th</sup> ed. 2000). Applicants respectfully submit that the cited references do not teach or suggest all the claim elements. Moreover, the Examiner has failed to establish the requisite motivation to combine the references with any reasonable expectation of success. For at least these reasons, a *prima facie* case of obviousness has not been established.

According to the Examiner, *Feldman* describes the use of anti-murine TNF- $\alpha$  antibodies to block TNF- $\alpha$  in a murine collagen induced arthritis (CIA) model of disease. *Office Action*, at 3-4. Based on these results, *Feldman* identifies TNF- $\alpha$  as an important target in rheumatoid arthritis, and notes that such results do "not exclude the possibility that blocking other cytokines may also yield considerable results." *Feldman*, at 254. *Feldman* briefly considers a number of other cytokines that are either induced or stimulated by TNF- $\alpha$ . These include IL-1, IL-2, IL-3, IL-4, IL-6, IL-8, IL-10, IFN- $\alpha$ , GM-CSF, TNF-receptor, RANTES, LT, MCAF, PDGF, GFE2, TGF- $\alpha$ , EGF, and PDGF A/B. *Feldman*, at 250, 252, and 253. Significantly, *Feldman* does not teach or suggest any role for IL-12 or IL-12 antagonists. *Feldman* does not teach or suggest a method for treating rheumatoid arthritis in a human subject comprising administering to said subject a therapeutically effective amount of an IL-12 antagonist that binds with IL-12, as presently claimed.

The Examiner contends that *Trinchieri* describes the importance of IL-12, and its stimulation of TNF- $\alpha$  in regulating immune responses and inflammation. *Office Action*, at 5. However, *Trinchieri* does not overcome the deficiencies of *Feldman*. Specifically, *Trinchieri* does not teach or suggest a method for treating rheumatoid arthritis in a

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human subject comprising administering to said subject a therapeutically effective amount of an IL-12 antagonist that binds with IL-12, as presently claims.

Based on the teachings in *Trinchieri*, the Examiner concludes that it would be obvious to treat rheumatoid arthritis by blocking IL-12, because this would result in a block of TNF-  $\alpha$ , as described by *Feldman*. *Id.* However, neither *Feldman* nor *Trinchieri* provide a motivation to combine their teachings. *Feldman* describes *in vitro* and *in vivo* experiments characterizing the role of TNF-  $\alpha$  in a murine CIA model of rheumatoid arthritis. See *Feldman*, at 250 and 252-253. In particular, *Feldman* reports that blocking TNF-  $\alpha$  with anti-TNF antibodies "ameliorated" the CIA condition in mice, as assessed by clinical score. *Feldman*, at 253. The results show that paw swelling, following injection of anti-TNF antibodies, was reduced from about 8% to about 25% over a 14-day period relative to negative controls. *Feldman*, at Figure 3. However, *Feldman* is almost exclusively limited to a discussion of TNF-  $\alpha$ . In this context, *Feldman* briefly discusses a number of other cytokines and antagonists of cytokines noted above (including a TNF-receptor that down regulates TNF-  $\alpha$ ). See *Feldman*, at 250, 252, and 253. Yet *Feldman* never even mentions IL-12 or antagonists of IL-12. Clearly, *Feldman* fails to provide any teaching that would motivate one of skill in the art to use an IL-12 antagonist to treat rheumatoid arthritis.

*Trinchieri* does not account for this deficiency. *Trinchieri* investigates the role of IL-12 in an immune response against bacterial infection concluding, "this cytokine offers promising possibilities for therapeutic use." *Trinchieri*, at 356. According to *Trinchieri*, the presence of IL-12 is important to achieve a proper immune response, including the production of IFN-  $\alpha$ . This conclusion is inferred from an experiment in which blocking

IL-12 with monoclonal antibodies suppressed the production of IFN-  $\alpha$  from between 60% to 90%, depending on the stimulus used. *Trinchieri*, at 362-3. *Trinchieri* suggests that IL-12 promotes the differentiation of Th1 helper cells, while repressing a Th2 response. *Trinchieri*, at 364-5. Thus, when IL-12 is inhibited, the normal Th1 response does not adequately develop in response to bacterial pathogens.

This reference discusses IL-12 only in the context of bacterial infections (stimulated by lipopolysaccharide (LPS) and *S. aureus*), not autoimmune disorders. More importantly, *Trinchieri* does not teach or suggest the use of IL-12 antagonists at all. In fact, the reference suggests just the opposite--to use IL-12 itself to treat disease. The anti-IL12 antibodies in *Trinchieri's* experiments were merely used to demonstrate the importance of IL-12 in fighting bacterial infections (*i.e.*, when IL-12 is inhibited, a proper immune response is not achieved). Thus, according to *Trinchieri*, IL-12 therapy would be useful to stimulate an immune response against foreign pathogens. Accordingly, *Trinchieri* suggests using IL-12 to treat HIV positive patients suffering from immune suppression (producing insufficient amounts of IL-12) in order to achieve a better immune response against bacterial infections. *Trinchieri*, at 365-6. According to *Trinchieri*, it is "important to determine whether NKSF/IL-12 treatment could shift the immune system more toward a Th1-like response, possibly improving its effectiveness against opportunistic infectious agents." *Trinchieri* at 366.

The Examiner states that "Figure 1 depicts some known function of IL-12." *Office Action*, at 5. Presumably, the Examiner relies on this figure to support some nexus between IL-12 and TNF- $\alpha$ . However, as shown in Figure 1, IL-12 induces TNF- $\alpha$  along with many other cytokines, e.g, IFN- $\gamma$ , GM-CSF, and IL-8. Modulation of cytokine

activity and expression involves a highly intricate set of cytokine, extracellular, and intracellular interactions. It is not proper to extrapolate the biological observation in *Trinchieri* regarding cytokine production to a statement that this reference makes obvious "a method of using an IL-12 antagonist (anti-IL-12), to block IL-12, which in turn decreases the production of TNF- $\alpha$  to treat RA in humans." Moreover, the Examiner's statement that "*Trinchieri et al.* teach the use of antibodies in the treatment of RA" is incorrect, because *Trinchieri* does not teach the use of antibodies to treat any autoimmune disease, let alone rheumatoid arthritis.

Clearly, *Trinchieri* fails to teach or suggest the use of any IL-12 antagonists, any therapy designed to inhibit IL-12, and any therapy directed to rheumatoid arthritis. In fact, *Trinchieri's* use of IL-12 as a therapy teaches completely away from the claimed invention, where IL-12 is being blocked with antagonists. Thus, the reference is being improperly cited against the claimed invention.

Given the teaching of *Trinchieri* to use IL-12 itself to stimulate an immune response against bacterial pathogens, and the teachings of *Feldman* to use TNF- $\alpha$  inhibitors to treat a murine model of rheumatoid arthritis, one of skill in the art would lack the necessary motivation to modify and combine these teachings to obtain the presently claimed invention.

Moreover, neither *Feldman* nor *Trinchieri* provide a reasonable expectation of success. *Trinchieri* fails in this regard for the reasons stated above. The reference is simply not relevant to using IL-12 antagonists to treat rheumatoid arthritis. Likewise, *Feldman* does not provide a reasonable expectation of success in using an IL-12 antagonist to treat rheumatoid arthritis. The reference is limited almost exclusively to a

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discussion of TNF-  $\alpha$ . *Feldman* briefly mentions IL-1, IL-2, IL-3, IL-4, IL-6, IL-8, IL-10, IFN-  $\alpha$ , GM-CSF, TNF-receptor, RANTES, LT, MCAF, PDGF, GFE2, TGF-  $\alpha$ , EGF, and PDGF A/B. *Feldman*, pages 250, 252, and 253. However, *Feldman* never discusses IL-12 or IL-12 antagonists. Moreover, the statement that "blocking TNF-  $\alpha$  does not exclude the possibility that blocking other cytokines may also yield considerable clinical benefits," *Feldman*, page 254, is mere speculation that does not teach or suggest a treatment of rheumatoid arthritis with IL-12 antagonists.

The Examiner's assumption that blocking IL-12 in bacterial infections would "obviously" result in a block of TNF-  $\alpha$  when applied in rheumatoid arthritis is conclusory and improper. *In re Lee*, No. 00-1158 (Fed. Cir. Jan. 18, 2002) (holding that the Board of Patent Appeals and Interference failed to meet the adjudicative standards for review under the Administrative Procedure Act). There is no teaching or suggestion in the art to this effect. In fact, quite the opposite is usually expected. As noted by *Feldman*, "virtually every cytokine known and assayable can be found in the RA synovium (Table 1)." *Feldman*, page 249. As the Examiner is no doubt aware, levels of TNF-  $\alpha$  are influenced by multiple different stimuli and cytokine mediators in the context of the intracellular environment. Thus, it is an oversimplification to argue that blocking one molecule (e.g., IL-12) in one intracellular context would "obviously" result in a block of another molecule (e.g., TNF-  $\alpha$ ) in a completely different context without actual evidence of such an effect.

At best, the Examiner has proposed an "obvious to try" scenario. However, "obvious to try" is not a proper basis for an obviousness rejection.

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For at least the stated reasons, the Examiner has failed to establish a *prima facie* case of obviousness. Reconsideration and withdrawal of the rejection are respectfully requested.

**CONCLUSION**

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims. The Examiner is invited to contact Applicants' representative to discuss the application.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: April 29, 2002

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